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Bristol-Myers Squibb Company

July 19, 2004

Dockets Management Branch
Food and Drug Administration, HFA-305
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2004D-0228; Guidance for Industry on Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV

Dear Sir or Madam:

Bristol-Myers Squibb (BMS) is a worldwide healthcare company, and our mission is to extend and enhance human life by providing the highest-quality pharmaceutical and related health care products. Among the medicines that we develop and distribute are those for the treatment of HIV disease. Consequently, we would like to offer the following comments on the above Draft Guidance.

1. **General Comments**

First, we applaud the FDA's efforts to clarify the regulatory expectations for fixed-dose combination (FDC) and co-packaged versions of HIV medicines. These efforts should help to accelerate the availability of these products to patients. We share the FDA's goal of facilitating distribution of combination therapies and improving patient compliance. The Draft Guidance provides a positive overall framework for evaluation of FDCs and co-packaged HIV drugs.

Second, our company is committed to helping make affordable HIV drugs available in sub-Saharan Africa. Part of this commitment is represented by the BMS Secure the Future initiative, under which over $100 million has been provided to build sustainable and reproducible programs to fight the HIV/AIDS pandemic in Africa. In addition in March 2001, we announced that BMS will not allow its patents to prevent access to inexpensive HIV/AIDS therapy in the sub-Saharan region. We are also willing to consider (on a case-by-case basis) providing a right of regulatory cross reference to our data if necessary to allow generic FDCs and co-packaged HIV drugs to be purchased by the U.S. government for distribution in sub-Saharan Africa. At the same time, we support the FDA's acknowledgement in this Guidance of innovators' patent and regulatory intellectual property rights within the United States.

Finally, we appreciate the FDA's efforts to learn more about potential obstacles to achieving the goal of more FDCs and co-packaged drugs, particularly for use in Africa. We offer to provide input and suggestions as requested to make the framework as successful as possible.

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Our comments on specific aspects of the Draft Guidance are set forth below.

2. Specific Comments

A. Intellectual Property

Section X.A; Attachment A

There are several statements in the Draft Guidance with which we strongly agree. It is noted in Section X.A. that if relevant products "are not developed by sponsors who either own or can obtain a right-of-reference to the underlying data, the regulations that govern the submission and approval of 505(j) and 505(b)(2) applications would apply." Attachment A further clarifies that, in Scenario 2, only a 505(b)(2) application would be acceptable (not an ANDA). Finally, it is noted that a 505(b)(2) application "would have to provide safety and efficacy data for the combination, either from studies the non-innovator conducted or from the literature, to support the approval of the combination."

We agree with the agency's position on this point. A 505 (b)(2) is a type of full NDA and can rely only upon:

- published literature
- studies conducted by the applicant

Such an application cannot rely on the data of an innovative company, without the innovator's consent. This is a fundamental difference between a 505(b)(2) application and a 505(j) ANDA.

That said, if a generic manufacturer will be seeking tentative FDA approval of an FDC or co-packaged HIV drug solely for distribution in Africa, BMS will favorably consider (on a case-by-case basis) providing a right of cross reference to certain data that might be needed for 505(b)(2) approval.

There is one point in Section X.A of the Draft guidance that requires further clarification. Scenario 1 in Attachment A outlines the regulatory requirements for innovative companies filing an NDA for a fixed-dose combination product. Scenario 2-4 outlines the requirements for non-innovator applicants. We are concerned that the CMC standards specified in the guidance for Scenario 2-4 may be lower than for Scenario 1. Specifically, innovative companies are advised to cross reference another application or a drug master file. Since non-innovative companies do not have access to current CMC documents, the quality standards for their manufacturing should be explicitly described.

Differences in the CMC standards applied to different applicants cannot be justified from a scientific and medical perspective. The nature and extent of data necessary to show that a combination product is bioequivalent to the individual component drugs is the same, regardless of the identity of the applicant. The FDA should identify the appropriate scientific and medical standard, and apply it to both Scenario 1 and Scenario 2.

B. Clinical Pharmacology and Biopharmaceutics
Section F. Dissolution Testing, page 9, line 342
We recommend adding a recognition that, although a single dissolution medium is desirable for a fixed dose combination product, it may not always be achievable. For these cases, the use of a second medium should be allowed.

C. Chemistry, Manufacturing & Controls
Section A. Applications Submitted for Co-Packaged Products, page 10
We recommend approval flexibility when the sponsor(s) is proposing a more protective blister co-package than is approved for one of the individual products. For example, sponsor A (product A) has FDA approval for Aclar blister package and sponsor B (products B & C) has approval for a more protective aluminum foil blister package. In this situation, available data suggests that actual stability data is not necessary on the aluminum foil dispensing package to support approval of the aluminum foil co-package for products A, B & C. A commitment could be made to provide stability data post approval.

In this section (lines 369-370), FDA appears to take the position that product stability in bulk shipping/storage containers should be required for submissions. We respectfully disagree. We believe that this is primarily a GMP issue. Instead, BMS recommends that the data be made available to the ORA field investigator or reviewing division upon request.

We also request that the FDA clarify the expectations of child resistance testing/requirements that support approval for packaging that will be used exclusively outside the United States (i.e., in Africa). The standards should be based on the WHO Annex 9 "Guidelines on packaging for pharmaceutical products," and not on the U.S. Consumer Products Safety Commission protocol for child resistant packaging.

D. Chemistry, Manufacturing & Controls
Section B. No. 3. Assurance of Reproducible Drug Release from the Dosage Form, page 11, line 407
Although a single dissolution medium is desirable for a fixed dose combination product, it may not always be achievable. For these cases, the use of a second medium should be allowed.

BMS appreciates the opportunity to provide comments and respectfully requests that FDA give consideration to our recommendations. We would be pleased to provide additional input as requested. Please call if you have any questions.

Sincerely,

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